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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/210,747	12/15/98	BRIGGS R	002957957

HM12/0219

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EXAMINER	
PORTNER, V	

ART UNIT	PAPER NUMBER
1641	4

DATE MAILED: 02/19/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/210,747	Briggs et al
Examiner	**Group Art Unit**
Portner	1641

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 12/15/98.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 34-37 is/(are) pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 34-37 is/(are) rejected.

☒ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

DETAILED ACTION

Claims 34-37 are pending.

Drawings

1. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

2. ***Sequence Letter***

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a) (1) and (a) (2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.136. In no case may and applicant extend the period of response beyond the six month statutory period and the response period is the time set in this action. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Double Patenting

3. Claims 34-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,849,305. Although the conflicting claims are not identical, they are not patentably distinct from each other because the now claimed vaccine comprising an aroA mutation represents is a genus claim of which the issued claims are a species; therefore the instant invention is an obvious variant of the previously patented invention as it comprises the characteristics of the issued compositions.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 recites the phrase "P. Haemolytica"; use of abbreviations is premissable in the claims once the word or phrase is defined in the claims.

Claim 36 recites the phrases "antigenic preparations thereof" and "other bacteria"; which antigens of what viruses which are included in the composition is not clear, and antigens need not be immunogenic and therefore the claim does not distinctly claim applicant's invention; what is meant by the phrase "other bacteria" is not clear as it is a member of a Markush group which recites members which are viruses and parasites.

The composition of the claims (34-37) do not recite an isolated or purified composition and naturally occurring bacteria with aroA mutations are possible, therefore the claims appear to claiming a product of nature.

Clarification is requested.

6. Claims 34-37 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to site directed mutations of *Pasteurella haemolytica* using aroA, PhaI, leukotoxin operon (C,A,B,D) and neuraminidase genes, and specific compositions for the treatment of cattle and sheep. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification teaches site-directed mutagenesis of specific regions within *Pasteurella haemolytica* but the claims recite the use of any region of the genome from *Pasteurella haemolytica*. It is not clear how any region of the genome can be used to produce a transformant which is viable; any random mutation in a plasmid would be expected to not result in a viable transformant. The specification is silent on how to use **any** region to the genome for producing a mutation to yield the desired result. The claim recites a method for producing a

mutation in a particular region but the specific regions are not recited; any region of the genome is claimed. It is not clear how any region would produce the desired mutant, without specific guidance the skilled artisan would not know how to use any region of the genome to obtain a desired mutant. It is also not clear how **any** mutation could be methylated by a methylating enzyme which inhibits endonuclease cleavage at the selected sites of GATGC and GCATC if the mutation did not contain these sights. Any mutation is being claimed, therefore the mutation is not required to have the methylation sites of GATGC and GCATC. Methods for producing mutations are known which comprise: isolating, introducing and screening transformants for a mutation. The specification does not teach how **any** mutation into **any** region of DNA of Pasteurella haemolytica would result in a stable transformant which could be screened. No working examples are provided with the missing information. Without such information the skilled artisan would not be able to use any region of the genome to make a transformant and would be required to preform undue experimentation to determine how to use **any** region of the genome to obtain a *Pasteurella haemolytica* mutants which could be screened.

7. Claims 34, 36 and 37 are is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to site directed mutations of *Pasteurella haemolytica* using aroA, PhaI, leukotoxin operon (C,A,B,D) and neuraminidase genes, and host cells but is not enabled for vaccines comprising the viral vectors for any antigen. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification fails to provide an enabling disclosure for the preparation and use of any viral compositions comprising nucleic acids encoding antigens because it fails to provide adequate guidance regarding how one would have prepared a nucleic acid which when introduced into a host would induce an immune response against the protein encoded by said nucleic acid. In contrast to direct protein immunogens, nucleic acids are required to target appropriate cell types within a host, become transcriptionally active, appropriately process any encoded proteins and present such proteins to the host in a manner suitable for recognition by the host's immune system. Such a "**gene therapy**" approach to epitope delivery suffers from all the limitations associated with gene therapy technology. However, as of 12/95, the artisan did not accept, in the absence of suitable and particular guidance, that such could have been accomplished

without having had to have exercised undue experimentation. See e.g. NIH Report Reference.

8. Claims 34, 36 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising site directed mutations of *Pasteurella haemolytica* using aroA, PhaI, leukotoxin operon (C,A,B,D) and neuraminidase genes, and host cells, does not reasonably provide enablement for the treatment of Pasteurella haemolytica along with any other infection because the specification does not provide original descriptive support for other compositions which may be used as effective vaccine compositions against multiple pathogens. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification fails to teach how to formulate and use the claimed vaccines against multiple pathogens. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to Staphylococcus epidermidis infection or disease induction. The specification teaches that the site directed mutations of *Pasteurella haemolytica* using

aroA, PhaI, leukotoxin operon (C,A,B,D) and neuraminidase genes, and host cells provide for attenuated cell lines which provide partial protection against wild type virulent strains. The specification suggests that the formulation of combination of different antigens together for the stimulation of an immune response but the specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity against multiple pathogens. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing both Pasteurella and viral or parasite or additional infections. No vaccines are known for the AIDs virus which is encompassed by the claims as now claimed as the use of any virus may be included in the composition. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced.

The ability to reasonably predict the capacity of an antigenic composition to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the at protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. See Boslego et al. wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum

antibody response I s induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

The specification fails to teach the identity of specific compositions which may be effectively used together with the claims Pasteurella haemolytica aroA mutant and together are able to induce protective immunity for both pathogens. Further, the specification fails to provide an adequate written description of how any viral, parasite or bacterial antigen could be used to provide protection against infection, the skilled artisan would be required to de novo locate, identify and characterize the claimed antigens for their protective characteristics prior to use. This would require undue experimentation given the fact that the specification is completely lacking in teachings as to other antigens which are useful in a combined composition for a combination vaccine against multiple pathogens with the claimed characteristics.

Claim Rejections - 35 U.S.C. § 103

9. Claims 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Homchampa et al (1992, reference submitted by Applicant).

Homchampa et al teach an attenuated aroA gene mutant of Pasteurella which was produced by insertion of a kanamycin-resistance gene into the aroA gene; a vaccine composition is also disclosed which provided complete protection against a lethal dose of Pasteurella

multocida when immunized mice were challenged parentally. Homchampa et al differs from the instantly claimed invention by failing to show a *Pasteurella haemolytica* mutant.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the techniques, methods and genes taught by Homchampa et al to transform *Pasteurella haemolytica* to obtain a vaccine composition comprising an attenuated live mutant of *Pasteurella haemolytica* because both *Pasteurella haemolytica* and *Pasteurella multocida* are of the same species of bacteria and Homchampa et al teach that the aroA gene from *Pasteurella multocida* showed a high degree of homology with the amino acid sequences of various other bacterial AroA proteins. The ordinary skill artisan would have had a reasonable expectation of success of obtaining an attenuated, live mutant which would provide protection against challenge because Homchampa et al show that mice immunized intraperitoneally with two does of live P. multocida aroA mutant were completely protected against a lethal parental strain challenge. Therefore in the absence of unexpected results, the ordinary artisan would have been able to obtain a Pasteurella haemolytica mutant which would provide protection against challenge following the guidance provided by Hemchampa et al.

10.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be changing February 7, 1998. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art 1641.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

vgp
February 8, 1999

James C. Housel 2/16/99

JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER